Alerts, Notices, and Case Reports

Aspergillar Myocarditis and Acute Coronary Artery Occlusion in an Immunocompromised Patient

MICHAEL K. HORI, MD
Sacramento, California
LAWRENCE L. KNIGHT, MD
PAULA G. CARVALHO, MD
DENNIS L. STEVENS, PhD, MD
Boise, Idaho

INVASIVE ASPERGILLAR infections have increased in frequency in proportion to the increasing number of severely immunocompromised patients. A characteristic of aspergillar infection is the invasion of blood vessels with resultant tissue necrosis.

Infections of the coronary arteries leading to vessel damage are rare. We report the case of a patient with aspergillar myocarditis in whom fatal acute coronary artery occlusion and myocardial necrosis developed with associated electrocardiographic and hemodynamic findings.

Report of a Case

The patient, a 45-year-old man, was admitted for increasing dyspnea, wheezing, and a productive cough of 12 hours' duration. The patient had suffered from severe asthma for 12 years, had required continuous corticosteroid therapy for the past six years, and had type II diabetes mellitus, treated with oral hypoglycemic agents. On physical examination, he appeared cushingoid and in moderate respiratory distress. The findings included a respiratory rate of 36 per minute with diffuse expiratory wheezes, decreased breath sounds, and fine right basilar rales. There were no abnormal cardiovascular findings. The laboratory evaluation revealed hypoxia, with blood gas determinations done with the patient breathing room air showing a Po_2 of 57 mm of mercury (7.58 kPa), a Pco_2 of 45 mm of mercury (5.98 kPa), and a pH of 7.46. The leukocyte count was 8.5×10^9 per liter (8,500 per μl) with 0.86 granulocytes, 0.06 band forms, 0.04 lymphocytes, and 0.04 monocytes. The chest radiograph did not show infiltrates, cardiomegaly, or congestive heart failure. The electrocardiogram showed sinus tachycardia with nonspecific ST-T wave changes. A sputum Gram's stain showed rare polymorphonuclear leukocytes. The initial sputum culture grew a few colonies of an *Aspergillus* species.

Despite aggressive therapy with bronchodilators, cefuroxime, corticosteroids, and diuretics, the patient required intubation because of respiratory failure and subsequently had intermittent fever. Cultures of blood and urine were sterile and of sputum grew *Pseudomonas maltophilia*. A regimen of the combination product trimethoprim and sulfamethoxazole was started intravenously, and a Swan-Ganz catheter was transiently placed that revealed a cardiac index of between 2 and 2½ liters per minute per m² with a normal pulmonary capillary wedge pressure (PCWP). On the 17th hospital day, transient hypotensive episodes developed with persistent fever, and the patient had a gradual fall in his leukocyte count, platelets, and hematocrit. Blood cultures remained sterile, and sputum smears were negative for acid-fast bacilli. The serum creatine kinase level was 25.0 μkat (1,500 IU) per liter and was exclusively of the MM isoenzyme. Specimens of bone marrow aspirate and biopsy were hypocellular in appearance but without evidence of neoplasia or infection. A regimen of broad-spectrum antibiotics was started, and the trimethoprim-sulfamethoxazole was stopped because of presumed medication-induced bone marrow toxicity. The patient remained febrile and neutropenic. A new, dense, right lower lobe pulmonary infiltrate and patchy, ill-defined infiltrates developed in both lungs, and a course of amphotericin B was initiated for presumed invasive aspergillosis. New unifocal ventricular premature contractions developed, and an episode of atrial fibrillation was also documented. A creatine kinase level was again high and showed exclusively the MM isoenzyme. Two days later the patient had refractory hypotension, with a cardiac index of 1 liter per minute per m² and a PCWP of 24 mm of mercury. His electrocardiogram at this time showed diffusely decreased voltage but no evidence of infarction. Despite ag-

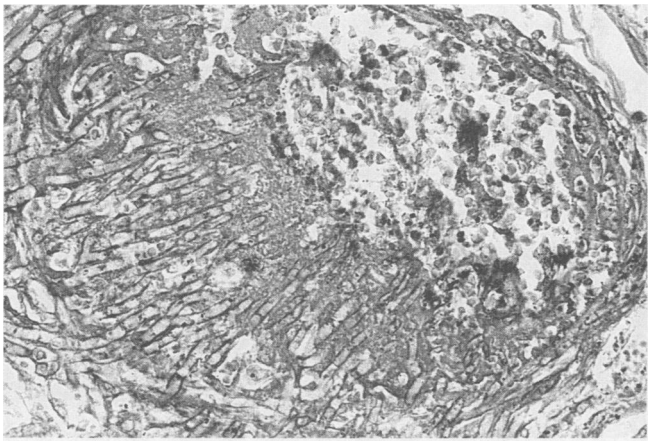

Figure 1.—The photomicrograph shows invasion and occlusion of a coronary artery by fungal organisms with branching septate hyphae (original magnification × 450).

TABLE 1.—*Infections Associated With Coronary Artery Invasion*

Endocarditis
Streptococcus viridans
Streptococcus faecalis or group D streptococcus
Salmonellal bacteremia
Syphilis *(Treponema pallidum)*
Kawasaki's disease
Aspergillus species
Falciparum malaria (thrombosis rather than invasion)

(Hori MK, Knight LL, Carvalho PG, Stevens DL: Aspergillar myocarditis and acute coronary artery occlusion in an immunocompromised patient. West J Med 1991 Nov; 155:525-527)

From the Department of Medicine, University of California, Davis (Dr Hori), the Department of Medicine, University of Washington School of Medicine, Seattle (Drs Carvalho and Stevens), and the Departments of Medicine (Drs Carvalho and Stevens) and Pathology (Dr Knight), Veterans Affairs Medical Center, Boise, Idaho.

Reprint requests to Dennis L. Stevens, PhD, MD, Chief, Infectious Diseases, Veterans Affairs Medical Center, 500 West Fort St, Boise, ID 83702.

TABLE 2.—*Location of Aspergillar Infections of the Heart*

Series	Patients, No.	Cardiac Locus of Infection			
		Endocardium	Pericardium	Myocardium	Myocardium Plus Endocardium and/or Pericardium
Walsh et al, 1980[7]	17	6	4	4	3
Atkinson et al, 1984[8]	11	1	0	6	4
Young et al, 1970[13]	7	0	2	2	3
Total cases (%)	35	7(20%)	6(17%)	12(34%)	10(29%)

gressive treatment with inotropic agents, the patient died that day.

At an autopsy, examination of the heart revealed that the epicardium and endocardium were free of lesions. The myocardium was homogenous except for a circular hemorrhagic area in the midportion of the intraventricular septum. On microscopic examination, the septum showed a broad zone of acute myocardial infarction marked by extensive myocardial and intravascular invasion by fungal organisms with branching septate hyphae consistent with an *Aspergillus* species. The involved vessel was occluded with thrombus (Figure 1). The rest of the heart and the coronary arteries were unremarkable. Extensive areas of friable, coarsely nodular consolidation were apparent in the pulmonary parenchyma of the left lower lobe and the entire right lung. Several areas of the pulmonary venous system were occluded with dark red thrombotic material. Microscopic examination of the areas of consolidation and thrombosis showed massive involvement by mycelial fungal organisms similar to those found in the heart. The blood vessels of the stomach were also occluded by fungal organisms with resulting mucosal necrosis.

Discussion

Coronary artery microbial infections with vessel damage are unusual. Bacterial mycotic aneurysms with thrombosis or rupture have been described as a complication of *Streptococcus viridans* and enterococcal bacterial endocarditis and of salmonellal bacteremia.[1-3] Medial necrosis of the aorta due to syphilis with the formation of saccular aneurysms may lead to coronary artery obstruction.[4] Kawasaki's disease, a disease of presumed but as-yet-unknown microbial origin, has been associated with coronary aneurysms in 17% of cases (Table 1).[5]

Fungal cardiac infections have been rare in the past but may be increasing in frequency.[6-14] *Aspergillus* species are less frequently identified in patients with heart infections than *Candida* species but are more common than *Mucor* or *Cryptococcus* species and invade the myocardium more frequently than do *Candida* species.[7,8,13] The immune systems of patients with cardiac aspergillar infections are usually compromised. Patients' risk factors include a cardiac or abdominal operation, broad-spectrum antibiotic treatment, immunosuppression from cytotoxic drug therapy, prolonged supraphysiologic corticosteroid therapy, malignant disease, diabetes mellitus, intravenous drug abuse, or prolonged vascular catheter placement.[6,10-12] Aspergillar myocarditis can occur from hematogenous seeding or as a result of spread from the endocardium (usually associated with prosthetic cardiac valve placement) or the pericardium (from contiguous pulmonary infections) (Table 2).[7-9,12,13,15] Myocardial involvement may be limited to rare small abscesses or may be associated with necrosis of large portions of the myocardium due to direct or vascular invasion with consequent ischemic necrosis.[13] Acute myocardial infarction recognized before the development of infection has been described previously in only seven patients.[14] By histopathologic examination, inflammatory infiltration with polymorphonuclear leukocytes is usually seen, but giant cells may be present or an infiltrate may be absent in patients taking cytotoxic drugs.[6,11,14]

This case illustrates some of the clinical aspects of aspergillar myocarditis. First, the contribution of myocardial disease to a patient's illness is often difficult to quantitate because of other contributing factors such as fungal pulmonary disease and drug toxicity.[13] Second, despite vessel involvement, blood cultures rarely show *Aspergillus* species.[6] Third, aspergillar myocardial disease may be associated with considerable hemodynamic compromise with a low cardiac index and a high PCWP,[13] and this may not respond to treatment with inotropic agents or antifungal drugs. Fourth, electrocardiographic changes are usually nonspecific despite extensive tissue damage and may be associated with a new onset of arrhythmias.[6,14] Finally, the creatine kinase MB isoenzyme may not be a useful method of detecting myocardial damage caused by *Aspergillus* species, possibly because of an overwhelming release of non-MB isoenzymes from other infected tissues.

In summary, invasive aspergillosis is one of the rare infectious diseases that may lead to coronary artery compromise. Aspergillar cardiac disease may be difficult to diagnose by current methods, does not respond to antifungal agents or cardioactive drugs, and has an extremely poor prognosis.

REFERENCES

1. Cliff MM, Soulen RL, Finestone AJ: Mycotic aneurysms—A challenge and a clue. Arch Intern Med 1970; 126:977-982

2. Crook BRM, Raftery EB, Oram S: Mycotic aneurysms of coronary arteries. Br Heart J 1973; 35:107-109

3. McGee MB, Khan MY: Ruptured mycotic aneurysm of a coronary artery. Arch Intern Med 1980; 140:1097-1098

4. Tramont EC: *Treponema pallidum* (syphilis), chap 194, *In* Mandell GL, Douglas RG, Bennet JE (Eds): Principles and Practice of Infectious Diseases, 2nd Edition. New York, NY, John Wiley & Sons, 1985, pp 1323-1333

5. Melish ME: Kawasaki syndrome: A new infectious disease. J Infect Dis 1981; 143:317-324

6. Williams AH: Aspergillus myocarditis. Am J Clin Pathol 1974; 61:247-256

7. Walsh TJ, Hutchins GM, Bulkley BH, Mendelsohn G: Fungal infections of the heart: Analysis of 51 autopsy cases. Am J Cardiol 1980; 45:357-366

8. Atkinson JB, Connor DH, Robinowitz M, McAllister HA, Virmani R: Cardiac fungal infections: Review of autopsy findings in 60 patients. Hum Pathol 1984; 15:935-942

9. Atkinson JB, Robinowitz M, McAllister HA Jr, Forman MB, Virmani R: Cardiac infections in the immunocompromised host. Cardiol Clin 1984; 2:671-686

10. Kammer RB, Utz JP: Aspergillus species endocarditis—The new face of a not so rare disease. Am J Med 1974; 56:506-521

11. Walsh TJ, Hutchins GM: Aspergillus mural endocarditis. Am J Clin Pathol 1979; 71:640-644

12. Walsh TJ, Bulkley BH: Aspergillus pericarditis: Clinical and pathologic features in the immunocompromised patient. Cancer 1982; 49:48-54

13. Young RC, Bennett JE, Vogel CL, et al: Aspergillosis: The spectrum of the disease in 98 patients. Medicine (Baltimore) 1970; 49:147-173

14. Kher HL, Ahuja IM, Rastogi DS, Dua SP: Primary disseminated aspergillosis involving myocardium: Review of literature with a case report. J Assoc Physicians India 1977; 25:433-436

15. Meyer RD, Fox ML: Aspergillus endocarditis: Therapeutic failure of amphotericin B. Arch Intern Med 1973; 132:102-106

Bilateral Spontaneous Renal Hemorrhage Due to Polyarteritis Nodosa

JOSEPH C. PRESTI, Jr, MD
New York, New York

PETER R. CARROLL, MD
San Francisco, California

POLYARTERITIS NODOSA is a progressive, necrotizing, inflammatory disease of the medium and small muscular arteries. The kidneys are the most common organs involved (70% to 80% of cases). Although the cause is unknown, much evidence supports an autoimmune origin, and an interesting subgroup of patients shares a history of intravenous methamphetamine abuse. The case reported here shows the importance of the aggressive medical treatment of the disorder.

Report of a Case

The patient, a 27-year-old woman with a history of intravenous methamphetamine abuse, was evaluated at an outpatient clinic for fever of several days' duration, anorexia, arthralgia, and right upper quadrant pain. The results of liver function tests were elevated: alkaline phosphatase 805 IU per liter (normal 4 to 133); aspartate aminotransferase (previously SGOT) 81 IU per liter (normal 7 to 39); the hepatitis B surface antigen (HBsAg) test was positive; and tests for the human immunodeficiency virus were negative. Ultrasonography showed a normal gallbladder and biliary tree. The patient was treated expectantly for a presumptive diagnosis of hepatitis.

Ten days later the patient was admitted to another hospital with fever and worsening upper quadrant pain. On physical examination, she had a temperature of 39.4°C (103°F) and right upper quadrant tenderness. The hematocrit was 0.30 (normal 0.36 to 0.46), leukocyte count 25×10^9 per liter (25,000 per μl; normal 3.4 to 10×10^9 per liter), but the serum creatinine value and results of a urinalysis were normal. An ultrasonogram showed a thickened gallbladder wall, and a regimen of intravenous antibiotics was begun for a presumptive diagnosis of acute cholecystitis.

Two days later, increasing abdominal and left flank pain developed, along with abdominal guarding and rebound tenderness. The hematocrit dropped to 0.21, and the patient became hypertensive. At laparotomy, 1 liter of brown ascitic fluid was removed and the liver was noted to be firm with a fibrinous exudate. The gallbladder appeared normal. Biopsy specimens were taken from the liver and enlarged mesenteric lymph nodes. The retroperitoneum was edematous.

The patient did well until the fourth postoperative day when she became acutely hypotensive and gross hematuria developed. The hematocrit was 0.08, and the serum creatinine value was 190 μmol per liter (normal 40 to 120). She was resuscitated with the administration of crystalloid and 6 units of packed erythrocytes. Computed tomography showed bilaterally enlarged kidneys with irregular, hypodense infiltrates that, by densitometric analysis, were consistent with intrarenal hemorrhage (Figure 1).

The patient was transferred to the University of California, San Francisco, Medical Center hemodynamically stable with a hematocrit of 0.28. Renal ultrasonography showed the right kidney to be 13 cm and the left kidney 20 cm long. A review of the liver and lymph node biopsy specimens showed focal necrotizing arteritis consistent with polyarteritis nodosa. The patient remained hemodynamically stable and was given corticosteroids (3 grams of methylprednisolone sodium succinate over three days) and a pulse dose of cyclophosphamide (750 mg per m^2). With therapy, the leukocyte count declined quickly from 51×10^9 per liter to a nadir of 1.7×10^9 per liter at day 16. Serum creatinine values peaked at 450 μmol per liter and stabilized at 240 μmol per liter. The patient's hypertension eventually responded to medical therapy. Magnetic resonance imaging was done before discharge and showed large, bilateral perinephric fluid collections of intermediate signal intensity on T1-weighted images that increased in signal intensity on T2-weighted images—consistent with resolving perinephric hematoma (Figure 2). Twenty days after the initiation of therapy, she was discharged on a maintenance dose of corticosteroids and cyclophosphamide. A year later, the patient was taking antihypertensive medications, had a serum creatinine level of 280 μmol per liter, and had no evidence of active polyarteritis nodosa.

Comment

Polyarteritis nodosa is a necrotizing, inflammatory disease of both medium and small muscular arteries. There is no age predilection, but it is more common in men than in women. Presenting symptoms include generalized constitutional symptoms as well as organ-specific signs and symptoms. Multiorgan involvement is common, with the kidneys being the most frequently involved. Indeed, renal disease

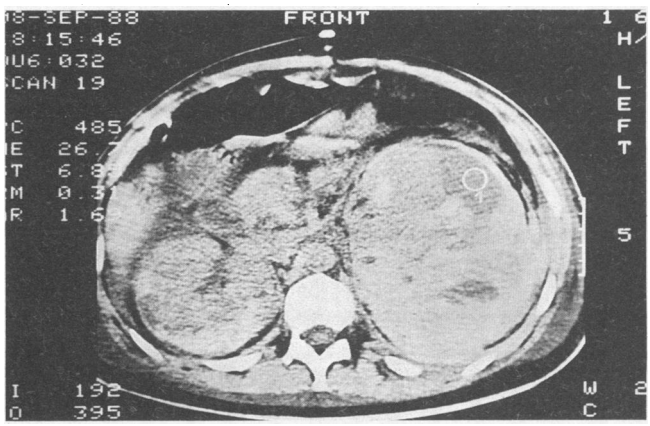

Figure 1.—A computed tomographic scan shows massive bilateral renal hemorrhage.

(Presti JC Jr, Carroll PR: Bilateral spontaneous renal hemorrhage due to polyarteritis nodosa. West J Med 1991 Nov; 155:527-528)

From the Department of Urology, University of California, San Francisco, School of Medicine. Dr Presti is now with the Memorial Sloan-Kettering Cancer Center, New York, New York.

Reprint requests to Peter R. Carroll, MD, Department of Urology, University of California, San Francisco, CA 94143-0738.